

PHARMACOPOEIA MONOGRAPH

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**Human coagulation factor VII**

**GPM.3.3.2.0002.15**

First Edition

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The present Pharmacopoeia Monograph applies to human coagulation factor VII preparations obtained from human plasma for fractionation.

Human coagulation factor VII is a protein fraction of human plasma that contains the single-chain glycoprotein coagulation factor VII and small quantities of the activated form of the double-chain factor VIIa derivative.

Human coagulation factor VII preparations may contain coagulation factors II, IX, and X, protein C and protein S, the content of which is determined in the released medicinal product. Human coagulation factor VII preparations contain no preservatives and no antibiotics.

MANUFACTURE

Plasma obtained from healthy donors and corresponding to the requirements of the Pharmacopoeia Monograph “Human plasma for fractionation” should be used for the manufacture of human coagulation factor VII preparations.

The manufacturing technology includes stages to eliminate or inactivate infectious pathogens. If any chemical compounds are used to inactivate viruses during the manufacturing process, their concentration should be decreased to a level that does not affect the safety of the medicinal product for patients. No antimicrobial preservatives are used in the manufacturing process. The manufacturing procedure should ensure that no activation of thrombin-forming coagulation factors is possible.

The medicinal product may contain stabilizers (albumin, polysorbate,

sodium chloride, sodium citrate, calcium chloride, glycine, lysine, heparin, antithrombin, etc.). Coagulation factor VII activity should be not less than 2 IU per milligramme of protein before any protein stabilizers are added. The medicinal product solution is packaged in primary containers using sterilizing filtration technique, freeze-dried, and closed under a vacuum or in an inert gas atmosphere.

## TESTS

**Description.** The medicinal product is an amorphous hygroscopic cake appearing as a white to pale yellow tablet or powder (unless different requirements are included in the Normative Document). The test is carried out by visual examination.

### Identification

**Species specificity.** Identity is confirmed by the presence of only human serum proteins. The test is carried out by gel immunoelectrophoresis, using sera against human, bovine, horse, and porcine serum proteins, as described in the General Pharmacopoeia Monograph “Agarose gel immunoelectrophoresis”. This test may also be performed with the gel immunodiffusion method, in accordance with the General Pharmacopoeia Monograph “Gel immunodiffusion”. The test should produce precipitation lines only with the serum against human serum proteins.

**Factor VII.** Demonstrated by the presence of factor VII activity. The test is carried out with the chromogenic method or by coagulometry, in accordance with the General Pharmacopoeia Monograph “Determination of blood coagulation factor activity”.

**Reconstitution time.** Not more than 10 minutes (unless otherwise specified in the Normative Document). A description of the method should be included, along with the solvent used, its volume, and the dissolution conditions (solvent temperature, need for mixing, etc.).

**Water content.** Not more than 2 %. The test is carried out with the Karl Fischer method, in accordance with the General Pharmacopoeia Monograph “Determination of water” (unless otherwise specified in the Normative Document).

The test method and the sample size necessary for the tests should be specified in the Normative Document.

**Particulate matter.** Visible particulate matter should be absent. The test is carried out in accordance with the General Pharmacopoeia Monograph “Visible particulate matter in medicinal products for parenteral use and ophthalmic dosage forms”. The Normative Document should include the name of the solvent, a description of the reconstitution technique, and (if necessary) the tested product preparation procedure.

**pH value.** From 6.5 to 7.5. The test is carried out by potentiometry, in accordance with the General Pharmacopoeia Monograph “Ionometry”.

**Osmolality.** Not less than 240 mOsmol/kg. The test is carried out in accordance with the General Pharmacopoeia Monograph “Osmolarity”.

**Protein content.** The content of protein per vial or millilitre of reconstituted solution should be specified in the Normative Document. The test is carried out using an appropriate method, in accordance with the General Pharmacopoeia Monograph “Determination of protein”.

**Heparin (for heparin-containing preparations).** Not more than 0.5 IU per 1 IU of coagulation factor VII. The test is carried out with the chromogenic method, in accordance with the General Pharmacopoeia Monograph “Determination of blood coagulation factor activity”.

**Thrombin.** Thrombin should be absent. The test is carried out by coagulometry, in accordance with the General Pharmacopoeia Monograph “Determination of blood coagulation factor activity” (the test for the absence of thrombin).

**Activated coagulation factors.** The coagulation time of each of the dilutions (1:10 and 1:100) should be not less than 150 seconds. The test is carried out by coagulometry, in accordance with the General Pharmacopoeia Monograph “Determination of blood coagulation factor activity”.

**Human coagulation factor VII activity.** Not less than 15 IU per millilitre of reconstituted solution. The test is carried out with the chromogenic method or

by coagulometry, in accordance with the General Pharmacopoeia Monograph “Determination of blood coagulation factor activity”.

**Specific activity.** Specific activity should be not less than 2 IU per milligramme of protein (in the absence of protein stabilizers).

The specific activity of the medicinal product is calculated according to the following equation:

$$\text{Specific activity} = \frac{\text{Coagulation factor VII activity}}{\text{Protein content}}$$

specific activity = coagulation factor VII activity / protein content

**Coagulation factor II activity.** Coagulation factor II activity, per vial or millilitre of reconstituted solution, should be specified in the Normative Document. The test is carried out with the chromogenic method or by coagulometry, in accordance with the General Pharmacopoeia Monograph “Determination of blood coagulation factor activity”.

**Coagulation factor IX activity.** Coagulation factor IX activity, per vial or millilitre of reconstituted solution, should be specified in the Normative Document. The test is carried out by coagulometry, in accordance with the General Pharmacopoeia Monograph “Determination of blood coagulation factor activity”.

Note

A reconstituted solution of the medicinal product is prepared for these tests (the reconstitution technique should be specified in the Normative Document of the manufacturer). If the formulation contains heparin, it should be neutralized by adding protamine sulfate: 10 µg of protamine sulfate per IU of heparin.

**Coagulation factor X activity.** Coagulation factor X activity, per vial or millilitre of reconstituted solution, should be specified in the Normative Document. The test is carried out with the chromogenic method or by coagulometry, in accordance with the General Pharmacopoeia Monograph “Determination of blood coagulation factor activity”.

**Stabilizer(s).** The stabilizer(s) added to the medicinal product is / are quantified using the methods described in the General Pharmacopoeia Monograph “Gas chromatography” and / or in accordance with the General Pharmacopoeia

Monograph “High-performance liquid chromatography (HPLC)” (unless a different method is specified in the Normative Document).

Acceptable limits for the content of stabilizer(s) should be specified in the Normative Document.

**Virus-inactivating agents.** The residual content of virus-inactivating agent(s) in the medicinal product is quantified using the methods described in the General Pharmacopoeia Monograph “Gas chromatography” and / or in accordance with the General Pharmacopoeia Monograph “High-performance liquid chromatography (HPLC)” (unless a different method is specified in the Normative Document). Acceptable limits for the content of virus-inactivating agent(s) should be specified in the Normative Document.

**Sterility.** The medicinal product is required to be sterile. The test is carried out in accordance with the General Pharmacopoeia Monograph “Sterility”.

**Pyrogenicity or Bacterial endotoxins.** The medicinal product is required to be non-pyrogenic, or its content of bacterial endotoxins should be not more than 0.1 EU per 1 IU of coagulation factor VII.

The test is carried out in accordance with the General Pharmacopoeia Monograph “Pyrogenicity” (not less than 30 IU of coagulation factor VII per kilogramme of animal body weight; the administered volume of the medicinal product should not exceed 10 mL per kilogramme of animal body weight) or in accordance with the General Pharmacopoeia Monograph “Bacterial endotoxins”, using the method described in the Normative Document.

#### **Viral safety**

**Hepatitis B virus surface antigen (HBsAg).** The medicinal product should contain no hepatitis B virus surface antigen. The test is carried out by enzyme immunoassay, using test systems approved for use in Russian health care practice and having a sensitivity not less than 0.1 IU/mL according to the Instructions for Use.

**Anti-hepatitis C virus antibodies.** The medicinal product should contain no anti-hepatitis C virus antibodies. The test is carried out by enzyme immunoassay,

using test systems approved for use in Russian health care practice and having 100 % sensitivity and specificity according to the Instructions for Use.

**Anti-human immunodeficiency virus (HIV-1 and HIV-2) antibodies and HIV-1 p24 antigen.** The medicinal product should contain no anti-human immunodeficiency virus (HIV-1 and HIV-2) antibodies and no HIV-1 p24 antigen. The test is carried out by enzyme immunoassay, using test systems approved for use in Russian health care practice and having 100 % sensitivity and specificity according to the Instructions for Use.

**Packaging and Labeling.** In accordance with the General Pharmacopoeia Monograph “Medicinal products containing human plasma”.

**Storage.** The medicinal product should be stored away from light, in the temperature range of 2 to 8 °C, unless otherwise specified in the Normative Document.